A Randomized Controlled Study of Accelerated Versus Standard Hepatitis B Vaccination in HIV-Positive Patients

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Background. In human immunodeficiency virus (HIV)–infected patients, the immunogenicity of hepatitis B vaccines is impaired. The primary and secondary aims of our study were to investigate the effectiveness and compliance of 2 different vaccination regimen in an HIV-infected population.

Methods. A noninferiority trial with a 10% response margin was designed. Included were patients ≥18 years old, with negative HBsAg/anti-HBc serology, and not previously vaccinated against hepatitis B. Patients were stratified according to CD4+ cell count: <200, 200–500, ≥500. Participants received 10 μg HBvaxPRO intramuscularly according to a 0–1–3 week schedule or the standard 0–4–24 week schedule. Anti-HBs levels were measured at week 28, considered protective >10 IU/L.

Results. Modified intention to treat analysis in 761 patients was performed. Overall response difference was 50% (standard arm) versus 38.7% (accelerated arm)–11.3% (95% confidence interval [CI], [4.3, 18.3]), close to the 10% response margin. In CD4+ cell count group 200–500 cells/mm3, the response difference was 20.8% (95% CI [10.9, 30.7]). However, the response difference in CD4+ cell count group ≥500 cells/mm3 was -1.8% (95% CI [-13.4, +9.7]). Compliance was significantly superior with the accelerated schedule, 91.8% versus 82.7% (P < .001).

Conclusion. In HIV-infected patients, compliance with an accelerated hepatitis B vaccination schedule is significantly better. The efficacy of an accelerated schedule proved to be non-inferior in CD4+ cell count group ≥500 cells/mm3.

Clinical Trials Registration. CT00230061.

Safe and effective hepatitis B vaccines have been commercially available since 1982. Human immunodeficiency virus (HIV)–infected patients carry a high risk of contracting hepatitis B virus (HBV). The response to hepatitis B vaccines in HIV-infected patients is, however, impaired. Trials in HIV-infected patients in the pre- and post highly active antiretroviral therapy (HAART) era have yielded response rates between 17% and 72% [1–8]. Response rate depended on various factors including CD4+ cell count, HIV load, and dosing schedule.

Optimal compliance to the vaccination schedule is essential to achieve effective seroprotection against HBV. However, poor adherence to the standard immunization schedule (0, 1, 6 months) is a matter of concern [9–12]. In healthy volunteers, accelerated hepatitis B vaccination has proven to be effective [13, 14]. We tested the hypothesis
that in unselected HIV-infected individuals an accelerated immunization schedule could have a positive impact on both the patient’s compliance and outcome of vaccination.

The present study was designed to evaluate the protective efficacy by measuring the antibody response to hepatitis B vaccine administered according to an accelerated immunization schedule in comparison to a standard schedule.

PATIENTS AND METHODS

Patients
We performed a large Dutch multicenter, parallel group, open label, randomized non-inferiority study. Participants were randomized to either an accelerated schedule (t = 0, 1 and 3 weeks) or the standard schedule (t = 0, 4 and 24 weeks). The primary endpoint was response measured by anti-hepatitis B surface antigen (anti-HBs) titer with a response margin of 10% difference. The secondary endpoint was comparison of the compliance between the two study arms. We offered HBV vaccination to all HIV-positive patients treated in 12 hospitals in the Netherlands that specialized in HIV treatment (Erasmus MC, Rotterdam; Haga Hospital, The Hague; Medical Center Haaglanden, The Hague; University Medical Center Utrecht, Utrecht; OLVG, Amsterdam; Maasstad Hospital, Rotterdam; St. Elisabeth Hospital, Tilburg; LUMC, Leiden; AZM, Maastricht; Rijnstate Hospital, Arnhem; VUMC, Amsterdam; Radboud Hospital, Nijmegen). Patients were included if they were ≥18 years old, with negative hepatitis B surface antigen (HBsAg) and anti-hepatitis B core (anti-HBc) serology, without active opportunistic infection, not pregnant at time of inclusion, and had not been previously vaccinated against hepatitis B. A randomization sequence was generated at the Erasmus MC by an independent investigator. Patients were stratified according to center and their CD4 cell count, assessed within the last 6 months, into 3 groups, <200, 200–500, and >500 cells/mm³. Patients were randomized in variable block sizes. At each center, sequentially numbered, opaque, sealed envelopes with the randomization label, randomized non-inferiority study. Participants were randomized into 3 groups, the standard group patients received a reminder for the last vaccination in the month prior to week 24. During this visit they were notified of the anti-HBs testing 4 weeks later.

When patients discontinued the vaccination schedule and response was not measured, they were excluded from the modified intention to treat (MITT) and the per protocol (PP) analyses.

The study protocol was approved by the local Medical Ethical Committee of all participating hospitals, and written informed consent was obtained from all subjects prior to study entry.

Assessments
Anti-HBs levels were measured on week 5 (initial response) and week 28 (long-term response) in the accelerated schedule and on week 28 in the standard schedule. Quantitative anti-HBs testing was performed by AxSym Ausab (Abbott Diagnostic Division), and the protective level of anti-HBs was defined as a titer ≥10 IU/L. At the time of vaccination we collected data on age, sex, transmission route of HIV infection, country of birth, weight, nadir CD4⁺ cell count, CD4⁺ cell count, plasma HIV-RNA level, and use of antiretroviral therapy. Undetectable viral load was defined as an HIV-RNA <50 copies/mL.

Statistics
Based on previous studies, we expected 50% protection against hepatitis B after initial vaccination in HIV-positive patients [1–8]. Sample size was calculated as 400 patients in each study arm to have a power of 80%, considering the accelerated group to be clinically noninferior to the standard group if the difference in response rate between the 2 groups was <10%.

The differences in response at week 28 between groups were calculated together with the 95% confidence interval (CI). Subgroup analyses were pre-specified for the CD4⁺ cell count stratification groups. The results are reported and interpreted according to the CONSORT statement on non-inferiority trials [15]. In addition, multivariate analysis of the treatment outcome was performed with logistic regression analysis. The data analysis was performed using SPSS for Windows, release 15 and SAS 9.2.

The analysis was performed in the MITT population and repeated in the PP population. In the MITT population patients with 3 vaccinations and an anti-HBs titer as endpoint beyond the stringent protocol time frame were included. The PP population included patients from the accelerated arm with the three vaccinations at the scheduled time points: vaccination 2 ± four days, vaccination 3 ± seven days, anti-HBs titer week 28 ± 28 days. The standard arm included patients with 3 vaccinations at the three time points: vaccination 2 ± 7 days, vaccination 3 ± 28 days, anti-HBs titer week 28 ± 28 days.

RESULTS

Patients
Between March 2004 and October 2007, 841 patients were randomized for the study and allocated to intervention into one of the study arms. Thirty patients were excluded from participation due to reasons depicted in Figure 1. Of the 811 patients receiving allocated intervention, 50 patients did not complete the study for various reasons and were excluded from analysis.
In the MITT, 761 patients were analyzed, and data of 569 patients were available for the PP analysis. In the accelerated arm 407 patients were allocated to intervention and 388 patients received allocated intervention. In the standard arm 434 patients were allocated, and 423 received the intervention. Patient characteristics in both groups were similar at baseline. Table 1 reports the distribution of age, sex, region of birth, body mass index, HIV risk, start CD4 cell count, nadir CD4 cell count, HIV-RNA, usage and duration of HAART, hepatitis A antibodies or hepatitis C coinfection. The variation in body mass index was small and within the normal range.

**Treatment Effect**

**Overall effect.** The overall response rate, defined as anti-HBs >10 IU/L, at week 28 in the standard arm and the accelerated arm was 50% and 38.7%, respectively. The immunogenicity results of the 2 vaccination schedules according to MITT and PP population analysis are depicted in Figure 2. The response difference in the overall MITT and PP analyses was 11.3% (95% CI [4.3, 18.3]) and 12.3% (95% CI [4.2, 20.4]), respectively. The 95% CI does not overlap 0; however, the difference is small and compatible with the noninferiority margin; therefore, inferiority cannot be concluded and the overall results were inconclusive. However, the treatment effect, that is, sufficiently high levels of anti-HBs in the accelerated versus standard vaccination schedule, differed significantly in the CD4 cell count >500 cells/mm³ group from that in the group with CD4 cell count 200–500 cells/mm³ (P = .0034 in the MITT analysis and P = .003 in the PP analysis) (Figure 2).

**Effect by CD4 cell count stratum.** The results showed that the response rates in the higher CD4 cell count groups (ie, 200–500 cells/mm³ and >500 cells/mm³) in both schedules were 33.5% (accelerated) versus 54.3% (standard) and 53.4% (accelerated) versus 51.7% (standard), respectively. In comparison, in the low CD4 cell count group these rates were 12.5% (accelerated) versus 27.1% (standard). The response differences in this noninferiority trial showed that the accelerated schedule was noninferior only in patients with CD4 cell count >500 cells/mm³ (2.1%; 95% CI [13.4, +9.7]). In patients with CD4 cell count 200–500 cells/mm³ the vaccination efficacy in the accelerated arm was inferior (response difference 20.8%; 95% CI [10.9, 30.7]) and in patients with CD4 cell count <200 cells/mm³ the result was inconclusive probably due to low patient numbers (Figure 2).

**Effect by baseline characteristics.** The following variables were associated with an overall better response (independent of treatment arm): high CD4 cell count, HAART use, female sex, undetectable HIV-RNA load (P<.001), and longer duration of HAART (≥4 years) (P = .03). CD4 cell count as a continuous variable showed a better response in favor of high CD4 cell count, the odds ratio (OR)_{standard} = 1.05 (95% CI [1.01,1.10])

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**Figure 1.** Flow chart of patients included in study. *HIV serology of baseline sample performed at first vaccination proved positive (n = 13 in accelerated arm and n = 6 in standard arm) **patients received no study medication (n = 4 in both study arms); patients withdrawal in (n = 2 in accelerated arm and n = 1 (pregnant) in standard arm). †† = died † acute hepatitis B infection (n = 1 in accelerated arm and n = 2 in standard arm); allergic reaction (n = 1 in standard arm).
The pinteraction between the ORstandard and ORaccelerated
5
.03.

Age as continuous variable also showed a better response in
favor of younger age (P = .008). After comparing patients
younger than 40 years to those 40 years or older, a similar
pattern in overall response was seen (P = .02). The effect of
treatment by baseline characteristics on the vaccination response
is shown in Figure 3.

In the CD4+ cell count >500 cells/mm3 group, where non-
inferiority was found, the effect of HAART use, female sex,
undetectable HIV-RNA load, younger age, and longer duration
of HAART remained significantly associated with an overall
better response (Figure 3A). After correction for these factors in
multivariable analysis, the noninferiority between the treatment
arms in the CD4+ cell count >500 cells/mm3 group was re-
tained. The difference between accelerated versus standard
arm in this CD4+ cell count group was 4.8% (95% CI

Table 1. Baseline Characteristics of Study Subjects with Received Allocated Intervention

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (n = 811)</th>
<th>Accelerated schedule (n = 388)</th>
<th>Standard schedule (n = 423)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years median (range)</td>
<td>40.0 (19–77)</td>
<td>40.0 (19–77)</td>
<td>40.0 (19–73)</td>
</tr>
<tr>
<td>Male, no. (%)</td>
<td>547 (67.4)</td>
<td>252 (64.9)</td>
<td>295 (69.7)</td>
</tr>
<tr>
<td>Region,a no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>453 (55.9)</td>
<td>216 (55.7)</td>
<td>237 (56.0)</td>
</tr>
<tr>
<td>2</td>
<td>137 (16.9)</td>
<td>66 (17.0)</td>
<td>71 (16.8)</td>
</tr>
<tr>
<td>3</td>
<td>37 (4.6)</td>
<td>18 (4.6)</td>
<td>19 (4.5)</td>
</tr>
<tr>
<td>4</td>
<td>164 (20.2)</td>
<td>76 (19.6)</td>
<td>88 (20.8)</td>
</tr>
<tr>
<td>5</td>
<td>20 (2.5)</td>
<td>12 (3.1)</td>
<td>8 (1.9)</td>
</tr>
<tr>
<td>Body Mass Index, no.; median(25th–75th percentile)</td>
<td>725; 24.0 (21.7–27.1)</td>
<td>343; 23.8 (21.7–27.1)</td>
<td>382; 24.1 (21.7–27.1)</td>
</tr>
<tr>
<td>HIV risk,b no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>322 (39.7)</td>
<td>157 (40.5)</td>
<td>165 (39.0)</td>
</tr>
<tr>
<td>2</td>
<td>447 (55.1)</td>
<td>212 (54.6)</td>
<td>235 (55.6)</td>
</tr>
<tr>
<td>3</td>
<td>12 (1.5)</td>
<td>6 (1.5)</td>
<td>6 (1.4)</td>
</tr>
<tr>
<td>4</td>
<td>9 (1.1)</td>
<td>4 (1.0)</td>
<td>5 (1.2)</td>
</tr>
<tr>
<td>5</td>
<td>2 (0.2)</td>
<td>0 (0.0)</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>7</td>
<td>19 (2.3)</td>
<td>9 (2.3)</td>
<td>10 (2.4)</td>
</tr>
<tr>
<td>Start CD4+ cell count; median(25th–75th percentile)</td>
<td>440 (290–610)</td>
<td>430 (290–610)</td>
<td>440 (290–623)</td>
</tr>
<tr>
<td>Start CD4+ cell count by category no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;200 cells/mm³</td>
<td>98 (12.1)</td>
<td>48 (12.4)</td>
<td>50 (11.8)</td>
</tr>
<tr>
<td>200–500 cells/mm³</td>
<td>399 (49.2)</td>
<td>185 (47.7)</td>
<td>214 (50.6)</td>
</tr>
<tr>
<td>&gt;500 cells/mm³</td>
<td>314 (38.7)</td>
<td>155 (39.9)</td>
<td>159 (37.6)</td>
</tr>
<tr>
<td>Nadir CD4+ cell count, no.; median(25th–75th percentile)</td>
<td>807; 200 (60–315)</td>
<td>385; 190 (60–299)</td>
<td>422; 200 (79–331)</td>
</tr>
<tr>
<td>HIV-RNA &lt;50 c/mL, no. (%)</td>
<td>475/811 (58.6)</td>
<td>231/388 (59.5)</td>
<td>244/423 (57.7)</td>
</tr>
<tr>
<td>On HAART, no. (%)</td>
<td>577 (71.1)</td>
<td>280 (72.2)</td>
<td>297 (70.2)</td>
</tr>
<tr>
<td>HAV positive antibodies, no. (%)</td>
<td>379 (46.7)</td>
<td>177 (45.6)</td>
<td>202 (47.8)</td>
</tr>
<tr>
<td>HCV-RNA positive, no. (%)</td>
<td>17 (2.1)</td>
<td>9 (2.3)</td>
<td>8 (1.9)</td>
</tr>
</tbody>
</table>

NOTE. a1West and East Europe, USA.
25Sub-Sahara Africa.
35Mediterranean.
45South and Central America, Caribbean.
55Asian.
15MSM (men having sex with men).
25Heterosexual.
35IV drugs.
45Blood–blood contact.
55Perinatal transmission.
75Unknown.

(P = .008) per increase of 50 CD4+ cells; the ORaccelerated = 1.13
(95% CI [1.08, 1.18]) (P < .001) per increase of 50 CD4+ cells.
The pinteraction between the ORstandard and ORaccelerated = .03.
Age as continuous variable also showed a better response in
favor of younger age (P = .008). After comparing patients
younger than 40 years to those 40 years or older, a similar
pattern in overall response was seen (P = .02). The effect of
treatment by baseline characteristics on the vaccination response
is shown in Figure 3.

Hepatitis B Vaccination in HIV Patients • JID 2011:203 (1 April) • 987
After correction for age, sex, and HIV-RNA load. HAART use is highly correlated to HIV-RNA load and could therefore not be entered into the same model. Correcting for HAART use instead of HIV-RNA load gave similar results.

Five-week time point in accelerated schedule. At week 5, samples from 332 of the 367 MITT patients in the accelerated arm were available for testing. In 53, 24, and 255 patients anti-HBs titers were $>10$ IU/L (positive responder), 3.0–9.9 IU/L (partial responder) and $<3.0$ IU/L (non-responder), respectively. From the positive responders at week 5, 47 (88.7%) patients subsequently had a protective titer at week 28. In the 255 nonresponders at week 5, 189 (74.1%) patients were still nonresponders at week 28. Nineteen out of 24 patients (79.2%) with a partial response at week 5 developed protective anti-HBs levels at week 28.

Compliance. Compliance was defined as receiving 3 vaccinations according to the per protocol definition with or without a measured anti-HBs titer as end-point. The compliance with both vaccination schedules was significantly higher in the accelerated arm, 91.8% (n = 356/388) versus 82.7% (n = 350/423) in the standard arm (P=.001). Of the 105 noncompliant patients, 10 patients stopped after the first vaccination; 16 patients stopped after 2 vaccinations, and 79 persons received 3 vaccinations but not within the time interval definition of the per protocol analysis. Younger patients were significantly more noncompliant (P = .006). All other baseline variables were not significantly different between the groups.

Adverse events. No serious adverse events were observed. One patient was advised to discontinue the vaccination schedule because of an allergic reaction (urticaria and dyspnoe) possibly related to the vaccination, a known side effect in $<.01\%$ according to the manufacturer manual. Local reaction in the deltoid region was incidental present but was not scored.

**DISCUSSION**

To our knowledge this is the first large prospective randomized study on efficacy of different hepatitis B vaccination schedules in adult HIV-positive patients. The results of our study show that the compliance with an accelerated schedule is significantly better than that with a standard schedule. Its efficacy is only noninferior in patients with CD4$^{+}$ cell count $>500$ cells/mm$^3$. This finding supports the use of an accelerated HBV vaccination schedule in HIV-infected patients with CD4$^{+}$ cell count $>500$ cells/mm$^3$. The observation that response to different hepatitis B vaccination schedules varies by CD4$^{+}$ cell count is a unique finding.
According to the present Dutch national guidelines on the management of HIV infection, HBV vaccination is offered according to a standard vaccination schedule (0, 1, 6 months) to all asymptomatic HIV-infected patients in several risk groups. This guideline includes all patients irrespective of the presence of several negative predictive factors of response, such as low CD4\(^+\) cell count or HIV-RNA load. The response rate to HBV vaccination in HIV-infected patients is known to be diminished [1–2]. However, the efficacy could be improved by proper timing of vaccine administration. In our study, undetectable HIV-RNA was found to predict a better response irrespective of the vaccination schedule. This is in agreement with prior results showing that undetectable plasma HIV-RNA at first HBV vaccination was found to predict success (OR 3.47; 95% CI [1.5,
increased likelihood of developing a response was associated with a CD4$^+$ cell count \( \geq 350 \text{ cells/mm}^3 \) \( (P = .008) \) in a previous study in 112 HIV infected patients [2]. This is in line with our own findings. A high CD4$^+$ cell count was associated with higher response rates.

Unlike most studies on HBV vaccination with a preponderance of males and MSM (men having sex with men), the majority of our study population consisted of heterosexuals and one-third of the population were female. This allowed us to analyze the influence of sex and risk group. Female sex turned out to be a predictor of better response. This confirms earlier published results [16, 17]. In contrast to previous published studies, membership of the MSM risk group was not a negative predictor for response. This could be explained by the composition of our population. Most study populations comprise a majority of males (MSM). Our population included 54% heterosexuals and 32% women. Younger age was found to be associated with a better response \( (P = .008) \), this was also documented in non–HIV-infected patients. However, younger patients are less compliant. It has been suggested that humoral and cellular immune function may decrease over years and result in diminished vaccine effectiveness in older individuals [18, 19].

Finally, usage of HAART was associated with development of a protective anti-HBs titer \( (P < .001) \). Moreover, longer duration of HAART showed a positive effect on response \( (P = .03) \). This may be explained by restoration of cellular immunity induced by antiretroviral therapy, resulting in reducing polyclonal B cell activation [20]. Untreated HIV infection is characterized by an immunologic dysfunction and a reduced ability to respond appropriately to antigens. Ongoing HAART probably results in qualitative improvement of cellular immunity, next to the increase in T cell count [21].

Despite identifying positive predictors of responding to vaccination, the overall response within both immunization schemes remains diminished. Poor results of HBV vaccination seen in different vaccination programs suggest the need for alternative strategies to prevent vaccination failure. Fonseca et al [2] studied the effect of double dosing HBV vaccination. They found a statistically significant higher seroconversion rate associated with double dose compared with standard dose in 36 of 56 patients with CD4$^+$ cell count \( \geq 350 \text{ cells/mm}^3 \) (64.3% \( \times \) 39.3%; \( P = .008) \). Rey et al [7] tested the hypothesis that doubling the number of hepatitis B vaccine injections might increase anti-HBs response rate. They assessed an increase in overall response from 55% after 3 vaccinations to 90% after 6 vaccinations (18 of 20 patients). In the study of Sasaki et al [8], 80 patients received double dose of recombinant HBV vaccine and received either GM-CSF or placebo with the first vaccine dose. They found a significant increase in the seroconversion rate in the GM-CSF group. In our study we tested an accelerated schedule versus the standard schedule and found a better overall response in favor of the standard schedule, except for the higher CD4$^+$ cell count group where noninferiority was found between the 2 treatment schemes with a better compliance in the accelerated schedule. The inferiority of the accelerated schedule in the lower CD4$^+$ cell count groups cannot be explained by a difference in HAART usage or the percentage of patients with undetectable HIV-RNA as they were equal in both groups. This is the first observation that response to different hepatitis B vaccination schedules varies by CD4$^+$ cell count. The underlying mechanism needs to be addressed in future studies. Perhaps the impaired immunity requires more time and longer intervals to benefit from repeated antigen stimulations.

Apart from the decreased response to HBV vaccination in HIV-infected patients, compliance to vaccination programs is poor irrespective of risk group. In our study, overall compliance proved to be significantly better in the accelerated schedule \( (P \leq .001) \). Completing a vaccination schedule contributes to providing protective antibody levels in those individuals at high risk of exposure to HBV, due to sexual behavior or traveling to HBV-endemic areas.

The strength of our study is the prospective randomized design and the large number of patients included. The population is heterogeneous reflecting day-to-day practice, and apart from a large number of MSM also comprises heterosexual patients and women. The high rate of HAART usage reflects a present-day HIV population and enables us to appreciate its value on the response to vaccination. The lowest CD4$^+$ cell count group represented only 12% of the study population.

In conclusion, patients with CD4$^+$ cell count \( > 500 \text{ cells/mm}^3 \) can be vaccinated against HBV according to an accelerated HBV schedule. Because compliance is significantly better in the accelerated vaccination arm, this schedule is preferable.

In all HIV-infected patients a better response rate is provided in patients on HAART with undetectable HIV-RNA load, longer duration of HAART use, female sex, and younger age. Delaying hepatitis B vaccination in HIV-infected high-risk groups under all circumstances according to the above-mentioned predictors of success may not be warranted, but our findings suggest a more optimized and individualized timing can be applied.

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